Arthritis, Guillain-Barré Syndrome, and Other Sequelae of *Campylobacter jejuni* Enteritis†

JAMES L. SMITH

ABSTRACT

The most frequently identified cause of gastroenteritis in developed countries is *Campylobacter jejuni*. In the United States, dairy products are the food sources commonly associated with outbreaks; however, most cases of *C. jejuni* gastroenteritis are sporadic, with poultry as the major source. Diarrhea, malaise, fever, and abdominal pain are the usual symptoms of *C. jejuni* enteritis. Lasting only a few days, the illness is generally self-limiting; however, some cases may be more severe. Although several virulence factors have been identified in *C. jejuni*, their role in disease is currently unclear. *C. jejuni* has been linked to the acquisition of certain forms of sterile arthritides such as reactive arthritis and Reiter's syndrome and to acute generalized paralytic diseases such as Guillain-Barré syndrome, Miller-Fisher syndrome, and Chinese paralytic syndrome. In addition, *C. jejuni* may induce diseases affecting the nervous system, circulatory system, and various organs, particularly in immunocompromised individuals. Illnesses associated with *C. jejuni* have been estimated to cost the citizens of the United States several billion dollars annually.

Key words: *Campylobacter jejuni*, Reiter's syndrome, reactive arthritis, Guillain-Barré syndrome, diarrhea

Campylobacter was recognized as an animal pathogen long before it was identified as a human pathogen responsible for gastroenteritis (*73*). In the early 1970s, Dekeyser et al. (*48*) and Butzler et al. (*33*) were the first to report the isolation of *Campylobacter* from stools. The realization that *Campylobacter* was a common cause of diarrhea was not appreciated in the early 1970s because of its unique growth requirements. Clinical laboratories at that time did not routinely culture specimens at 42°C under reduced oxygen tension (*225*).

Dekeyser et al. (*42*) and Butzler et al. (*33*) diluted stools with broth, passed the supernatant fluid through 0.65-μm millipore filters, plated the filtrate on thioglycollate fluid agar containing blood and antibiotics, and incubated the plates at 42°C. Using this technique, *C. jejuni* was isolated from the stools of 45 of 900 (5.0%) diarrheic patients. The significance of these studies, however, was not recognized until the late 1970s.

In the United Kingdom, Skirrow (*213*), using a less elaborate technique (an agar medium containing antibiotics and incubation under 5% O_2: 10% CO_2—85% H_2 atmosphere at 43°C), found that 57 of 803 (7.1%) diarrheic patients had stools positive for *C. jejuni*, while 194 controls had negative stools. Using a similar technique, Blaser et al. (*21*), in the United States, found that 5.1% of diarrheic patients had positive stools, whereas the stools of healthy individuals were negative for *C. jejuni*. It was quickly recognized that many outbreaks of *Campylobacter* enteritis had a food origin. From 1978 to 1986, 45 of 57 (79%) of *Campylobacter* outbreaks in the United States were foodborne (*36*). Most of these outbreaks were probably caused by *C. jejuni* since approximately 90% of the reported *Campylobacter* isolates are *C. jejuni* (*36*).

GASTROENTERITIS

Campylobacter jejuni is probably the most frequently identified cause of acute infectious diarrhea in developed countries (*214*). The organism is the most commonly isolated bacterial enteric pathogen in the United States (*233*), and in England and Wales, the isolation of *Campylobacter* exceeds that of *Salmonella* (*215*). In industrialized nations of Europe, North America, and Australia, *Campylobacter* affects individuals of all ages; however, peaks of incidence occur in children < 4 years of age and in young adults 20 to 30 years of age (*215*, *233*). The incidence is much higher in developing countries and most children become immune by 2 years of age. Therefore, in developing countries, *Campylobacter* enteritis is rarely seen in adults (*215*, *234*).

Epidemiology of Campylobacter *enteritis in the United States and Canada*

For the period 1973 to 1987, there were 53 identified foodborne outbreaks of campylobacteriosis in the United States, with 1,547 cases and 2 deaths (*17*). Dairy products accounted for 25 of 53 outbreaks (47%) and chicken, turkey, and eggs were implicated in 4 outbreaks. There were 1,869 reported outbreaks of bacterial foodborne disease in the United

States during the period 1973 to 1987. *Campylobacter* accounted for 2.8% (53 of 1,869) of those outbreaks and 1.4% (1,547 of 108,906) of the total bacterial foodborne cases (*17*). Bean and Griffin (*17*) reported the factors that contributed to the *Campylobacter* outbreaks in the United States: 67% involved obtaining the food from unsafe sources and 45% of the outbreaks involved improper holding temperatures, inadequate cooking, contaminated equipment, and/or poor personal hygiene of the food handler.

Canadian authorities started reporting *C. jejuni* outbreaks in 1980, and from 1980 to 1984 there were 47 outbreaks with 713 cases (*240*). Dairy products accounted for 29 of 47 (62%) of the outbreaks and poultry accounted for 4 of 47 outbreaks. In Canada, there were 785 outbreaks of microbial foodborne disease; campylobacteriosis accounted for 6.0% (47 of 785) of the outbreaks of microbial origin and 4.1% (713 of 17,601) of the total cases (*240*).

Although dairy products (including raw milk) accounted for many of the *Campylobacter* outbreaks in Canada and the United States, poultry is considered to be the major source of the organism. Sporadic cases of *Campylobacter* enteritis vastly outnumber the cases seen in outbreaks and poultry is believed to be responsible for many of the sporadic cases (*110, 224*). Harris et al. (*95*) estimated that 48% of campylobacteriosis cases were due to consumption of chicken.

Transmission and sources of Campylobacter

Volunteer studies indicate that the infectious dose for *C. jejuni* is low, i.e., ≤500 organisms (*36*). Although such a low infective dose would suggest that person-to-person transmission should readily occur, it seems relatively uncommon.

Campylobacteriosis can be considered a zoonotic disease since *Campylobacter* is a common commensal in wild and domestic birds and animals (*71, 224*). Direct transmission from animals can occur in those individuals whose occupations place them in close contact with animals. Urban dwellers may become infected by contact with pets, particularly puppies and kittens excreting *Campylobacter* (*197, 215*). However, direct transmission from animals appears to account for few infections.

Most cases of the disease result from indirect transmission of *Campylobacter* from animals via milk, water, or meat. Milk and water can easily become contaminated by animal feces; both unchlorinated water and unpasteurized milk have caused outbreaks of campylobacteriosis (*71, 215, 224*). Red meats and offal can become contaminated with *Campylobacter* during slaughtering and dressing of carcasses (*73*); however, thorough cooking of meats will destroy the organism. The $D_{55°C}$- value for *C. jejuni* is approximately 1 min (*218*). Colonization of poultry with *Campylobacter* is common, and during the slaughter procedure, *C. jejuni* from intestinal contents of colonized birds can spread to other carcasses (*215, 224*). Handling raw poultry and subsequent cross-contamination of other foods as well as eating of undercooked poultry are the most common causes of campylobacteriosis (*36*).

Raw clams and oysters have been implicated in cases of *Campylobacter* enteritis but raw seafood appears to be infrequent as a cause of disease in spite of the fact that contaminated water has caused outbreaks (*1*).

An outbreak of *Campylobacter* enteritis has been attributed to a salad containing raw vegetables (*22*). *C. jejuni* has been isolated from raw vegetables obtained from farmers' markets but not from supermarkets (*175*). The use of unchlorinated farm water to clean vegetables or the use of manure and sewage as fertilizer for vegetable crops may result in vegetable contamination (*175*). Koenraad et al. (*122*) demonstrated that elimination of *Campylobacter* spp. during sewage treatment was not complete; the organisms could be isolated from both sedimented sludge and surface water at the discharge points of sewage plants. The spreading of this sludge containing *Campylobacter* on crop lands could contaminate vegetables and other crops. It is possible that the use of untreated water from sewage plants as drinking water for animals or in irrigation also could be a source of contamination.

Virulence mechanisms

Inconsistent results with in vitro virulence assays and the lack of a completely satisfactory animal model has confused the role of virulence factors in campylobacteriosis. Certain strains of *C. jejuni* produce a cytolethal, nondialyzable protein which is trypsin sensitive and heat labile. The cytotoxin is not immunologically cross-reactive with Shiga, cholera or *Clostridium difficile* toxins (*88, 148*). Ruiz-Palacios et al. (*196*) were not able to find an association between cytotoxin production and *Campylobacter* diarrhea.

C. jejuni toxin (CJT) is similar to cholera toxin (CT) and to the labile toxin of enteropathogenic *Escherichia coli* (*45, 230*). When anti-CT antibody was used to detect CJT, the sensitivity was about 0.001 of that of the anti-CT reaction with CT, indicating that CJT and CT are not completely homologous. Both CT and CJT bind to gangliosides but they differ in the type of ganglioside bound (*230*). A strong association between CJT production and campylobacteriosis has been demonstrated by Ruiz-Palacios et al. (*196*). However, Perez-Perez et al. (*177*) and Konkel et al. (*125*) were unable to demonstrate the presence of CJT in *C. jejuni*. Proposed enterotoxin-encoding sequences in *C. jejuni* DNA could not be shown using various oligonucleotide primers and the polymerase chain reaction (PCR) (*125*). The negative results reported by Perez-Perez et al. (*177*) and Konkel et al. (*125*) indicate that further studies are needed to determine the role of CJT in campylobacteriosis.

Cytolethal distending toxin (CLDT) is produced by strains of *C. jejuni*. Under the influence of CLDT, HeLa cells, Chinese hamster ovary cells, and Vero cells slowly distend and then die. The toxin appears to be a nondialyzable, trypsin-sensitive and heat-labile protein (*109*). The effect of CLDT on cells is not neutralized by antisera against Shiga-like toxins or heat-labile enterotoxins (LT) of *E. coli*. The role of CLDT in disease is unknown. A similar toxin is produced by *E. coli* strains (*181*).

Adherence of *Campylobacter* to epithelial cells is related to an outer-membrane protein which preferentially attaches to host cell membranes (*66*). Flagella and lipopolysaccharide (LPS) also may play roles in the adherence of *Campylobacter* to intestinal epithelial cells (*158*). In addition, *Campylobacter* LPS binds to intestinal mucus gel (*158*).

Flagella and motility appear to be important factors for the virulence of *C. jejuni*. There are two nearly identical flagellin genes (*fla*A and *fla*B) arranged in a head-to-tail repeat separated by an intergenic region. The two genes are 95% identical at the nucleotide level (*173*). A^+B^+ organisms are motile, have long flagella and have 100% invasive capacity. Organisms with an inactivated A gene are nonmotile, have short flagella and their invasive capacity is only 1% that of A^+B^+ strains. Strains with an inactivated B gene are motile, have long flagella and their invasive capacity is 98% that of A^+B^+ organisms (*173*). Strains in which both A and B genes are inactivated are nonmotile, have no flagella and have 0.5% of the invasive capacity of A^+B^+ strains. These data indicate that flagella, motility, and intact *fla*A in *C. jejuni* are necessary for invasion of intestinal cells. Motility allows the cells to move actively toward intestinal crypts or surfaces thus promoting colonization, adherence, and invasion (*173*).

Iron increases the virulence of *C. jejuni* in mice (*114*) and is required for the production of CJT (*153*). Iron is necessary for the growth of *Campylobacter* on bacteriological media (*16*) and the aerotolerance of the organism is enhanced in iron-containing media (*226*). Free iron is limited in mammalian hosts and the mechanisms by which invading pathogens acquire iron is an important aspect of infection (*146*). Therefore, the means by which bacteria acquire iron can be considered virulence mechanisms (*83*). *Campylobacter* spp. do not produce detectable amounts of siderophores (low-molecular-weight iron-chelating compounds). By having the proper membrane receptors and scavenging siderophores produced by other intestinal bacteria, the organisms acquire iron while in the intestinal tract (*16*). In low-iron media, hemin, hemoglobulin, hemin-hemopexin and hemoglobin-haptoglobin stimulated the growth of *C. jejuni* (*180*). Hemopexin and haptoglobin are serum proteins that bind hemin and hemoglobulin, respectively. The mechanism by which *Campylobacter* strains acquire iron from these complexes is not known. In addition, Pickett et al. (*180*) found that transferrin, ferritin, and lactoferrin were unable to provide iron to the organism. *Campylobacter* strains produce hemolysin (*10*, *180*) that does not appear to be iron-regulated (*180*). The roles that iron, hemin, hemoglobulin, and hemolysin might play in virulence of *C. jejuni* have not been determined. However, iron dextran greatly enhances the virulence of the organism in a neonatal mouse model (*114*).

Superoxide dismutase (SOD) protects bacteria against oxidative stress and may contribute to the survival of intracellular pathogens, since macrophages can kill ingested bacteria by oxidative mechanisms (*184*). Both *C. jejuni* and *Campylobacter coli* produce a SOD with an iron cofactor. Pesci et al. (*179*) demonstrated that *C. jejuni* required SOD for entry into cultured intestinal cells and for intracellular survival. It is probable that the iron-SOD complex protects the organism during invasion of epithelial cells and prevents oxygen-mediated intracellular killing (*179*).

Thus, virulence factors are present in strains of *C. jejuni*; however, their relationship to diarrhea and disease is obscure. More studies are needed to elucidate the roles of these virulence factors in the pathogenicity of *Campylobacter*.

Clinical aspects of enteritis

The manifestations of *C. jejuni* enteritis are not particularly distinctive or readily differentiated from gastroenteritis caused by other enteric pathogens. The prodromal phase (symptoms which signal approaching disease) with fever, headache, myalgia (muscle pain), and malaise (generalized discomfort or uneasiness) is present 12 to 48 h before onset of diarrhea. The diarrhea is often accompanied by cramping abdominal pain and can be severe enough to mimic appendicitis. The pattern of diarrhea varies from loose stools to profuse, bloody, slimy and/or foul-smelling stools. Vomiting does not appear to be a major symptom. Generally, these symptoms are self-limiting and may persist from one day to a week or longer. While most patients recover within a week, 20 to 25% of the patients suffer relapses or prolonged illness (*21*, *34*, *72*). Most patients recover without medical intervention; however, in severe or protracted cases, antibiotics should be used. In the United States, dehydration due to *C. jejuni* diarrhea is seldom encountered. When dehydration does occur, fluid and electrolyte replacement is necessary (*21*).

Patients with AIDS appear to be more susceptible to *Campylobacter enteritis*. A survey conducted in Los Angeles County indicated that the average incidence of campylobacteriosis in AIDS patients was 519 of 100,000, as compared to the crude general population rate of 13.3 of 100,000 (*219*). AIDS patients infected with *Campylobacter* had a shorter survival time than AIDS patients without *Campylobacter* infections. A similar picture is probable for individuals with other immunocompromising conditions.

ARTHRITIS

Reactive arthritis is the acute, inflammatory, sterile arthritis which develops days or weeks after an infection which originated at a nonarticular site. Reiter's syndrome is a subtype of reactive arthritis in which there is a triad of symptoms: arthritis, urethritis, and conjunctivitis (*69*). These diseases are triggered by either enteric or urethral infections. An important feature of the reactive arthritides is that the diseased joint is sterile. The triggering organisms are not isolated from the joint or joint fluids and rheumatoid factor is not present. However, elevated levels of antibody to the triggering organism are present in the host.

The triggering organisms include the enteric pathogens *C. jejuni*, *Salmonella typhimurium*, *S. enteritidis*, *Shigella dysenteriae*, *S. flexneri*, *S. sonnei*, *Yersinia enterocolitica*, or *Y. pseudotuberculosis*. Other salmonellae also may induce arthritis but are seldom encountered. Urogenital infections caused by *Chlamydia trachomatis* or *Ureaplasma ureolyticum* also may induce reactive arthritis (*141*, *216*). Common features shared by reactive-arthritides-inducing bacteria include: the organisms infect mucosal surfaces, have LPS on their outer membranes, and are intracellular parasites (*117*, *150*).

Clinical characteritics of the reactive arthritis and Reiter's syndrome

Seven to 30 days after an intestinal or urethral infection, an inflammatory arthritis signals the beginning of reactive

arthritis. An average of three joints are affected; the arthritis is asymmetric and generally involves the articulations of the lower extremities. The knee is commonly affected and the joint may contain large amounts of fluid. Smaller joints may be involved and carpal tunnel syndrome may result when the wrist is affected. Spinal involvement may occur with the common complaint of lower back pain. Inflammation of the ligament-bone junctions is often seen with the common expression of swelling of the fingers or toes. Swelling and tenderness in the synovium along the bones between the interphalangeal joints result in swollen ("sausage") digits. Extraarticular manifestations include keratodermia blennorrhagica in which scaling lesions appear on palms and soles. Urethritis with dysuria and a thin, watery discharge also may be seen in patients with reactive arthritis (*69*).

Reiter's syndrome is triggered by the same infecting organisms. Reiter's syndrome consists of (1) asymmetric poly- or oligoarthritis in knees and ankles, sausage digits, swelling at the Achilles tendon insertion, tenderness at the plantar fascia insertion, and low back pain; (2) nonspecific urethritis manifested by dysuria and a thin, watery discharge; and (3) unilateral or bilateral conjunctivitis. Balanitis circinata (inflammation of the glans penis) with hyperkeratotic lesions at the junction of the glans and shaft of the circumcised penis is present in 25 to 50% of men with Reiter's syndrome. Keratoderma blennorrhagica (scaling lesions on soles and palms) and oral lesions may be present and there may be cardiac involvement (*69*, *258*).

The symptoms of reactive arthritis or Reiter's syndrome generally subside within 4 to 5 months. Unfortunately, a small but significant number of patients have lengthy recoveries of 12 months or longer or have persistent or relapsing illnesses (*141*).

While proteins from gram-negative enteric bacteria share peptide sequences with regions of the HLA-B27 antigen (*207*), this molecular mimicry between HLA-B27 and bacterial antigens does not appear to provide an adequate explanation for the role of HLA-B27 in arthritis (*117*).

Pathology of reactive arthritis and Reiter's syndrome

How does an infection at a distant nonjoint site induce a disease in joints? The diseased joints are sterile, i.e., viable organisms are not present; however, antigens from the triggering organism are found. Antigen migration to the afflicted joints has not been explained satisfactorily (*150*). Mononuclear cells consisting of $CD4^+$ and $CD8^+$ T lymphocytes (CD4 and CD8 are diagnostic surface antigens), monocytes, and B lymphocytes are found in the synovial membrane from reactive arthritis patients, which indicates that cellular immune responses are important in the disease (*100*). Synovial $CD4^+$ T-cells from arthritic patients proliferate in vitro in response to the triggering microorganism with the production of cytokines. The cytokine secretion pattern of the T-helper cells is that of the T_H1 type, i.e., gamma interferon and interleukin-2 are produced. The T_H2 subtype, which produces other cytokines, is not seen (*100*, *117*, *216*). The T_H1 subtype executes cell-mediated immune responses, whereas the T_H2 subtype assists in antibody production for humoral immune responses (*208*). Diseases are often associated with a dominant $CD4^+$ T-helper cell subtype and the increased level of T_H1 cells with its particular cytokine pattern may promote arthritis in susceptible individuals (*100*). Hermann et al. (*101*) have isolated HLA-B27 restricted cytotoxic $CD8^+$ T-cells from synovial fluids of reactive arthritis patients which have a specificity for antigens of arthritogenic enterobacteria. Destruction of bacterial antigen-containing HLA-B27 phagocytic cells by activated cytotoxic $CD8^+$ T-cells may lead to cytokine release, attraction of other inflammatory cells such as T_H1 cells, and induction of arthritis (*101*).

In contrast to cellular immunity, humoral immunity does not appear to play a major role in reactive arthritis or Reiter's syndrome. Antibodies against antigens from triggering enteric microorganisms can react with homologous regions of the HLA-B27 molecule in vitro (*207*). However, enteric bacteria which are not arthritis triggering also cross-react with antibodies against HLA-B27 (*117*). Since MHC Class I antigens such as HLA-B27 are present in virtually all somatic cells of $HLA\text{-}B27^+$ individuals, it is difficult to explain why only a few tissues such as synovium and tendon insertions are attacked if antibodies against bacterial antigens can also react with HLA-B27 antigen (*117*). Currently, there is little evidence of a role for humoral immunity in the pathogenesis of reactive arthritis and Reiter's syndrome.

While current studies indicate that T-cells may be involved in the pathogenesis of reactive arthritis and Reiter's syndrome, there are more unanswered questions than answers (*100*, *101*): What types of T-cells are involved in the cause and resolution of arthritis? Are the T-cells which respond to arthritogenic bacteria preferentially activated in the synovium or are they recruited from outside and migrate to the already inflamed joint? What is the nature of the bacterial antigen or self-antigen which is recognized by the T-cells? Why are $HLA\text{-}B27^+$ individuals more susceptible to arthritogenic effects of certain bacteria? Why do the majority of $HLA\text{-}B27^+$ subjects who become infected with arthritogenic bacteria fail to develop arthritis? Why does arthritis develop in individuals who do not carry the HLA-B27 antigen?

Role of HLA

Predisposition to reactive arthritis and Reiter's syndrome triggered by gastroenteritis and genital infection is strongly associated with the presence of HLA-B27 antigen of the host's major histocompatibility complex (MHC). Approximately 2% of the individuals who are infected with a triggering microorganism will develop arthritis; roughly 20% of infected $HLA\text{-}B27^+$ individuals will become arthritic. Approximately 80% of the reactive arthritis and Reiter's syndrome patients are $HLA\text{-}B27^+$ (*5*, *69*, *216*). It is unclear why the $HLA\text{-}B27^+$ individual is more susceptible to arthritis; however, it has been determined that carriage of the HLA-B27 antigen influences the development of arthritis, its severity, and the extent and duration of symptoms (*115*).

While proteins from gram-negative enteric bacteria share peptide sequences with regions of the HLA-B27 antigen (*207*), this molecular mimicry between HLA-B27 and bacterial antigens does not appear to provide an adequate explanation for the role of HLA-B27 in arthritis (*117*).

Treatment of reactive arthritis and Reiter's syndrome

The reactive arthritides can be treated with nonsteroidal antiinflammatory drugs, intraarticular injection of steroids, and/or physical treatment. The use of antibiotics is controversial. While short-term treatment of postenteric reactive arthritis with antibiotics does not appear to be beneficial, antibiotic treatment in chlamydial infections reduces the risk of postvenereal arthritis (*141*, *231*).

Role of Campylobacter

A preliminary bout of diarrhea was reported in all of the *Campylobacter*-induced cases of arthritis listed in Table 1. Patients ranged in age from 5 to 76 years and 18 of 29 patients were male. The HLA-B27 antigen was present in 15 of 29 patients and an additional patient carried HLA-B7 antigen which cross-reacts with HLA-B27 (*4*). Thus, more than half of the patients were of the HLA-B27 haplotype.

TABLE 1. *Reported cases of reactive arthritis or Reiter's syndrome following* Campylobacter *enteritis*

No. Cases (sex), age	Diarrhea	*C. jejuni* isolated	HLA-B27	Reference
1 (M), 20y[a]	+	stool	+	(*18*)
1 (M), 30y	+	stool	–	(*246*)
1 (F), 36y	+	stool[b]	–	
1 (M), 22y	+	stool	+	(*142*)
2 (M), 20y and 51y	+	stool	+	(*185*)
3 (F), 21y, 43y, and 39y	+	stool	+	
1 (F), 45y	+	stool	–	
1 (F), 36y	+	stool	–	(*91*)
1 (M), 55y	+	stool	?	
4 (M), 25y, 33y, 41y, and 56y	+	stool	+	(*131*)
1 (F), 18y	+	stool	+	
1 (M), 76y	+	stool	–	
1 (M), 26y	+	stool	?	
1 (F), 32y	+	stool	+	
1 (F), 31y	+	stool	+	(*211*)
4 (M), 41y, 5y, 7y and 9y	+	stool	–	(*107*)
1 (F), 29y	+	stool	–	
1 (M), 34y	+	stool	+[c]	(*58*)
1 (M), 46y	+	stool	–	(*59*)
1 (F), 25y	+	stool	+	(*31*)

[a] Abbreviations: y, age in years; F, female; M, male.

[b] *Campylobacter* species not identified.

[c] Patient was HLA-B7; HLA-B7 antigen cross reacts with HLA-B27 antigen.

Eastmond et al. (*58*) reported that 133 individuals were infected with *C. jejuni* following an outbreak of milk-borne campylobacteriosis due to a power failure at a milk pasteurization plant. Gastroenteritis was present in 88 of these individuals but only 1 individual who was HLA-B7$^+$ demonstrated symptoms of reactive arthritis. In a second outbreak of campylobacteriosis in which food was the suspected vehicle, 86 of 106 guests at a party were examined. Thirty-five of these individuals had symptoms of gastroenteritis with *C. jejuni* positive stools or serology, 31 did not have gastroenteritis but were seropositive for *C. jejuni*, and 20 did not show signs of infection (*31*). One patient, a woman who was HLA-B27$^+$ with a positive stool for *C. jejuni*, developed reactive arthritis.

There appears to be nothing in the literature concerning the nature of the arthritogenic factor(s) of *Campylobacter*. The LPS of arthritis-triggering salmonellae have been demonstrated in synovial fluid cells or synovium of reactive arthritis patients (*150*). LPS can stimulate lymphocytes to produce cytokines which are active in inflammation; therefore, LPS is believed to be an arthritogenic antigen for salmonellae. *C. jejuni* also produces LPS antigens (*164*) and it is possible that *C. jejuni* LPS are arthritogenic.

GUILLAIN-BARRÉ SYNDROME

The Guillain-Barré syndrome (GBS), an acute inflammatory demyelinating polyneuritis marked by paralysis, pain, and wasting muscles, has replaced poliomyelitis as the most frequent cause of acute neuromuscular paralysis in developed countries (*162*, *194*). Worldwide, the annual incidence of GBS is 1 to 2 of 100,000 persons (*194*); the annual incidence in the United States is 1.7 of 100,000 (*165*). Although approximately 15% of patients recover completely, the remaining surviving patients suffer varying degrees of physiological, neurological, or physical deficits, and 3 to 8% of the patients die (*194*).

Clinical characteristics of GBS

GBS is seen 1 to 3 weeks after an antecedent event (Table 2) and may begin with paresthesia (abnormal sensations such as burning, pricking, tickling, or tingling) and dysesthesia (impairment of touch sensation) of toes or fingertips. Generally, weakness begins in the legs and spreads to the upper extremities as well as to the respiratory, facial, and oropharyngeal musculature. There may be pain in the large muscles of the thigh, flank, or back. In severe cases, the disease can affect respiration, eye movements, swallowing, or autonomic functions (*162*, *189*, *194*). The patient is generally bedridden because of general paralysis.

Pathology of GBS

Inflammatory lesions scattered throughout the peripheral nervous system are present in GBS, but the central nervous system is spared. These lesions are characterized by macrophages invading the myelin sheaths which surround the nerve fibers, leading to demyelination. The macrophages enter between the lamellae and strip myelin from intact axons. Electrophysiological studies indicate that most GBS patients show reduced nerve conduction velocity and conduction block (reduction in the amplitude of muscle action potential) indicative of demyelination (*163*, *194*, *236*). Axonal loss may be found.

Both humoral and cellular immune mechanisms are probably involved in GBS; however, the successful treatment of GBS with plasmapheresis and immunoglobulin has led to an emphasis on the role of humoral immunity. Demyelination of nerve tissue occurs when sera from patients with acute GBS are injected into rat sciatic nerve (*32*, *67*, *96*, *198*), but sera

from recovered patients did not have the demyelinating effect (*96*). Lymphocytes from GBS patients did not produce demyelination of rat sciatic nerve (*67*). However, Winer et al. (*251*) were unable to demonstrate significant demyelination of rat sciatic nerve with sera from GBS patients.

TABLE 2. *Antecedent events associated with Guillain-Barré syndrome*

Antecedent event	References
Bacterial infection	
Borrelia burgdorferi	(*30, 103, 151*)
Campylobacter	this review
Mycoplasma pneumoniae	(*79, 93*)
Salmonella typhi	(*199*)
Viral infection	
Adenovirus	(*93*)
Cytomegalovirus	(29, 52, 53, 93, 251)
Enterovirus 71	(*7*)
Epstein-Barr virus	(*52, 85*)
Hantavirus	(*64*)
Hepatitis A, B, C, and non-A, non-B viruses	(*119, 147, 232*)
Human immunodeficiency virus	(*80*)
Human T-cell lymphotropic virus type III	(*44*)
Japanese encephalitis virus	(*187*)
Measles virus	(*144*)
Vaccination	
Live measles vaccine	(*85*)
A/New Jersey influenza vaccine	(*205*)
Oral polio vaccine	(*118, 242*)
Human diploid cell rabies vaccine	(*26, 120*)
Plasma-derived hepatitis B vaccine	(*210*)
Synthetic hepatitis B vaccine	(*241*)
Hemophilus influenzae type B diphtheria toxoid-conjugate vaccine	(*47, 77*)
Measles-mumps-rubella vaccine	(*168*)
Tetanus toxoid	(*182*)
Drugs	
Captopril	(*37*)
Zimeldine	(*65*)
Ofloxacin	(*204*)
Streptokinase	(*41, 60, 140*)
Bovine gangliosides	(*68, 137, 138, 171, 206*)
Immunosuppressive drug FK506	(*249*)
Miscellaneous	
Surgery	(*147*)
Jellyfish stings	(*174*)
Wuchereria bancrofti (filariasis)	(*20*)

Anti-peripheral-nerve myelin antibodies are found in GBS patients and are highest when neurological symptoms appear; declining antibody titers against peripheral-nerve myelin correlate with clinical improvement (*127, 129, 130, 244*). These anti-peripheral-nerve myelin antibodies exert their demyelinating action through complement activation. Using heat-inactivated sera from GBS patients with added fresh complement, demyelination in dorsal root ganglion tissue culture was demonstrated (*127*). The C7 component of complement was necessary for demyelination, which indicated that the attack phase of the complement cascade is involved.

Willison and Kennedy (*247*) determined that 27% of 847 GBS patients exhibited high levels of antibodies to gangliosides and that the major ganglioside involved is GM_1. The presence of IgA, IgM, and IgG antibodies against the GM_1, GM_2 and GD_{1b} gangliosides was demonstrated in sera of GBS patients (*19, 105, 212*); such patients appear to have a poor prognosis. Complement fixation and inflammation of neural tissue by anti-ganglioside antibodies may induce the pathology seen in GBS patients (*247*). The putative role of antibody and complement in human demyelinating neuropathies, including GBS, has been reviewed (*128*).

T-cell responses to peripheral nerve proteins may have a function in the pathogenesis of GBS (*116*). There is proliferation of T-cells and increased levels of soluble interleukin-2 receptors (sIL-2 R) in GBS (*98*). Increased serum concentrations of sIL-2 R indicate the presence of circulating activated T-cells, which may be relevant to GBS pathogenesis. Helper/inducer T-cells may assist B-cells in the production of antibodies against myelin components. In a delayed-type hypersensitivity reaction, activated T-cells may recruit macrophages which attack the myelin sheath or may act as cytotoxic cells against myelin (*97*). Serum levels of the cytokine, interleukin-2 were markedly increased in GBS patients and as patients recovered from the disease, the level of the cytokine returned to normal (*98*). These findings suggest that interleukin-2 has a pathogenic role in GBS.

Honavar et al. (*102*), citing postmortem findings, proposed that T-cells may be the major cause of demyelination in some GBS patients, whereas antibody-mediated demyelination may be more important in other patients. T-cell and B-cell responses generally act in concert, and the different pathologies seen in GBS probably reflect the relative contribution of each cell type (*102*). However, there is a scarcity of information concerning the role of cellular immunity in GBS and more intensive studies are needed to elucidate the role of T-cells and their products in the pathogenesis of GBS.

Role of HLA

Several investigations were conducted to determine whether or not a relationship between HLA haplotype and susceptibility to GBS exists. In studies involving 280 GBS patients, susceptibility was not related to the HLA haplotype (*3, 113, 139, 228, 250*). Other studies, involving 70 patients, suggest that the HLA haplotype may play a role in the disease. Susceptibility to GBS was associated with HLA-A1, -B8, -DRw3 and -Dw3 (*2*), HLA-DR3 (*8*) or HLA-B35, -B51 and -Bw52 (*261, 262*). The number of GBS patients in these studies was small and it seems premature to state that there is or is not a relationship between HLA haplotype and susceptibility to GBS.

Variants of GBS

Miller-Fisher syndrome (MFS) is an acute, self-limiting neuropathic disorder characterized by ophthalmoplegia (paralysis of eye muscle), ataxia (muscle incoordination), areflexia

(absence of reflexes), and facial weakness. MFS accounts for approximately 5% of GBS cases and except for ophthalmoplegia, the clinical features overlap with GBS (*70, 191*). Al-Din et al. (*6*), however, consider MFS to be a brain-stem syndrome rather than a variant of GBS. Antibodies to GQ_{1b} ganglioside are present in most cases of MFS (*40, 248, 263*). A factor in sera of MFS patients, probably the anti-GQ_1b antibody, may be responsible for muscle weakness (*191*). Initially, the serum factor increases the spontaneous release of acetylcholine from the motor nerve termini, followed by the abolition of spontaneous and nerve-evoked acetylcholine release. Botulism has a clinical syndrome similar to that of MFS and botulism toxins also bind to GQ_{1b}; thus, the toxins of *Clostridium botulinum* and the anti-GQ_{1b} antibodies of MFS patients bind to the same ganglioside receptor (*247*). Sera from MFS patients were neurotoxic to dorsal root ganglia neurons from young rats and resulted in death of the neurons (*259*). Plasmapheresis treatment leads to recovery of patients with MFS (*160, 263*); intravenous serum globulin also is effective (*227*).

Chinese paralytic syndrome (CPS; also known as Acute Motor Axonal Neuropathy) is easily confused with GBS; CPS differs from GBS in that the disease has a summer seasonality, usually involves children, and occurs predominantly in rural areas of northern China. GBS does not show seasonality and both children and adults contract the disease, although the median age at onset of GBS is 50, and individuals from both rural and urban settings are susceptible (*156,157,268*). Whereas CPS can not be distinguished from GBS clinically, it can be by electrodiagnosis. In CPS, there is little evidence of demyelination; the disorder may result from a lesion in a reversible distal motor nerve terminal or anterior horn cell (*156, 157*). Similarly to GBS, high titers of IgG anti-GM_1 are present in patients with CPS (*126*). Since cases similar to CPS have been reported elsewhere in the world, the disease is probably not limited to China (*157*). However, Yan and Guohua (*257*) do not think that CPS is a variant of GBS but that it is actually a variant of poliomyelitis caused by an altered poliovirus. The use of oral poliovirus vaccine may have led to an alteration in poliovirus pathogenicity or allowed a minor, infrequent poliovirus strain to develop into an epidemic strain.

Treatment of GBS

Recovery is slow, requiring several weeks to months. Many GBS patients require extended and scrupulous intensive care including positive-pressure ventilation in cases with respiratory failure, nutritional support via nasogastric tube feeding, prevention of pressure on peripheral nerves, and prevention of nosocomial (hospital-acquired) infections. Most patients need physical and occupational therapy as well as strong psychological support (*162, 194, 195*).

Although administration of corticosteroids was considered an effective treatment for GBS, it is no longer judged to be beneficial (*162, 194*). Plasmapheresis or plasma exchange can be efficacious if used early during the course of the disease (*74, 90, 155*). Intravenous administration of immune serum globulin has been shown also to aid in recovery (*154, 170, 209*); however, other workers have reported high relapse rates with intravenous immunoglobulin use (*35, 106*). In a large study involving approximately 150 patients, van der Meche et al. (*160*) determined that intravenous immunoglobulin administration was as effective as plasmapheresis in the treatment of GBS. It is interesting that the treatment for GBS involves opposing interventions: plasmapheresis depletes the body pool of immunoglobulin whereas intravenous immunoglobulin injection expands it. The benefits of plasmapheresis probably result from the removal of harmful antibodies such as demyelinating antibodies (*237*). Why the administration of intravenous immunoglobulin is effective is not clear. Intravenous immunoglobulin treatment is advantageous in that it does not require the sophisticated equipment and trained personnel necessary for plasmapheresis. Although children with GBS have been successfully treated using plasmapheresis (*63*), administration of intravenous immunoglobulin is considered to be a safer pediatric procedure (*154, 160, 209*). While plasmapheresis and intravenous immunoglobulin aid in the recovery of GBS patients, supportive care and rehabilitation of the patient are of primary importance (*56*).

Antecedent events leading to GBS

In one-half to two-thirds of GBS cases, the syndrome follows an infection (*194, 252*). Both viral and bacterial infections have been implicated as antecedent events leading to GBS (Table 2). Hankey (*93*) obtained serological evidence indicating that herpes simplex and herpes zoster viruses, parainfluenza virus, Coxsackie virus, echo virus, coronavirus and influenza A and B viruses also may be associated with GBS. Bacterial infections associated with GBS include *Borrelia burgdorferi*, *Campylobacter* species, *Mycoplasma pneumoniae* and *Salmonella typhi* (Table 2) and *Shigella boydii* (*93*). However, presence of *B. burgdorferi* antibodies in GBS patients may be coincidental (*169*). Filariasis caused by *Wuchereria bancrofti* also may be a possible antecedent infection (*20*). Although an association has not been made, it is probable that an even larger number of viruses, bacteria and parasites trigger GBS.

Vaccinations also can lead to GBS (Table 2). Interestingly, while there was a significant increase in the number of GBS cases following the 1976 to 1977 influenza vaccination with A/New Jersey vaccine, no such increase occurred with a different vaccine used in 1978 to 1979 (*12, 104, 205*). Presumably, influenza vaccines used since 1980 have not been associated with GBS. Uhari et al. (*242*) and Kinnunen et al. (*118*), in Finland, showed that administration of oral polio vaccine led to GBS in children; however, GBS in United States children after vaccination with oral polio vaccine has not been observed (*186*).

A number of drugs are related to GBS, including bovine gangliosides as treatment for neurological diseases; captopril treatment for hypertension; zimeldine, an antidepressant; ofloxacin, a fluoroquinolone antibiotic; streptokinase, a fibrinolytic activator; and FK506, an immunosuppressive drug used in transplant recipients (Table 2). However, there may be some question about the roles of streptokinase (*11*) and bovine ganglioside treatment (*84, 152, 200*) as antecedent events in GBS.

In up to 10% of GBS cases, surgery appears to be a trigger for GBS (*147*). The inducer is probably a subclinical microbial or viral infection resulting from the operation rather than the surgical process itself (*147*). Blood transfusions during surgery, if the blood is contaminated with a virus, may precipitate GBS.

It appears that a variety of antecedent events can trigger GBS; however, Dowling and Cook (*52*) caution that an apparent close association of an infection or another antecedent event with GBS in an individual does not necessarily imply that there is a biological association between the event and GBS.

Role of Campylobacter

GBS and MFS can result from *Campylobacter* gastroenteritis (Table 3). In the cases listed in Table 3, the presence of campylobacteriosis was demonstrated by stool isolation or positive serology and all cases presented with diarrhea prior to GBS or MFS. Blaser et al. (*23*) indicated that some patients with CPS were seropositive for *C. jejuni*. Thus, *C. jejuni* enteritis can be the antecedent event for GBS, MFS or CPS. Using stool isolation, serology, enzyme-linked immunosorbent assay (ELISA), or immunoblot, a number of workers (*29, 62, 87, 111, 135, 166, 222, 244, 252*) have shown that the incidence of *C. jejuni* infection prior to appearance of GBS ranged from 13 to 49% with a mean of 29%.

Anti-ganglioside antibodies are found in about 27% of GBS cases (*247*). Some GBS patients with *C. jejuni* antibodies also have ganglioside antibodies and it is believed that these patients have a more serious disease with severe axonal degeneration and a poor prognosis (*121, 245, 266, 267*). Vriesendorp et al. (*244*) found that poor recovery in GBS correlated with serological evidence of *C. jejuni* infection but did not correlate with ganglioside antibodies. Enders et al. (*62*) did not find a correlation between GBS severity, axonal degeneration, and outcome of the disease with presence or absence of a humoral immune response to *C. jejuni* or gangliosides. Severe axonal damage, anti-ganglioside antibodies and antecedent *C. jejuni* infection do not form a clinical triad and these factors can occur in GBS independently of one another (*160*). Therefore, GBS triggered by a *C. jejuni* infection does not necessarily result in a poorer outcome for patients (*62, 220, 256*).

The incidence of *C. jejuni* gastroenteritis is high, yet GBS is rare, suggesting that only a few serotypes of *C. jejuni* may be responsible for GBS (*111*). A group of Japanese workers showed that a specific serotype of *C. jejuni* (Penner serogroup *19*) was associated with a significant number of GBS cases in Japan (*76, 135, 259*). A German group found that *C. jejuni*-specific antibodies in GBS patients were predominantly directed against the Lior 11 serotype (*62*), although the most common serotype found in gastroenteritis in Germany is Lior 4. In both the German and Japanese studies, the number of patients was small and, obviously, more studies are needed to determine if only certain serotypes of *C. jejuni* are associated with GBS. The lipopolysaccharides of a number of serotypes of *C. jejuni*, 0:1, 0:4, 0:19, 0:23, and 0:36, bear structural similarities to glycosphingolipids of nerve gangliosides (*13,14, 15, 259, 264, 265*). The resulting molecular mimicry between bacterial and nerve antigens may play a role in *C. jejuni* induction of GBS, but proof is lacking.

A few proposals can be advanced as possible explanations for the triggering of GBS by *C. jejuni*, although there is no evidence supporting any triggering mechanism. (1) There is mimicry between LPS components of *C. jejuni* and components of nerve gangliosides. An antibody against a *C. jejuni* component may well attack a component with similar chemical structure in peripheral nerve tissue (*11, 189, 253*). (2) Several studies suggest that the genetic background (HLA haplotype) of certain individuals may predispose them to GBS (*2, 82, 259, 262*). When such individuals are infected with *C. jejuni*, GBS is a possible sequela. Yuki et al. (*260, 264*) and Sugita et al. (*229*) have demonstrated a close relationship between GBS and infection by *C. jejuni* serotype O:19 and HLA-B35 haplotype in Japanese patients. However, the sample size was small and the significance of these findings is uncertain. (3) *C. jejuni* may trigger GBS by producing a superantigen which activates T-cells to act as demyelinating agents (*189*). T-cells appear to play a role in GBS (*97, 98, 102*) but there is no evidence that *C. jejuni* produces a toxin or compound that behaves as a superantigen. Superantigens are microbial products that produce vigorous nonspecific proliferation of certain subsets of antigen-specific T-cells with massive release of cytokines; such uncontrolled activity may lead to disease (*203*). (4) Cholera toxin is known to bind to gangliosides (*112*) and some strains of *C. jejuni* produce a labile toxin similar to cholera toxin which also binds to gangliosides (*45*). The ganglioside-toxin complex could alter recognition of host self-antigens and trigger the immune system to attack gangliosides of the nervous system (*165, 189*, 221). However, it must be reiterated that nothing is known about the GBS triggering mechanism(s) of *C. jejuni*.

OTHER SEQUELAE OF *C. JEJUNI* INFECTION

In addition to arthritis and GBS, other nonintestinal diseases have been demonstrated as sequelae of *C. jejuni* infection (Table 4). These include diseases that affect the neurological system, skin, gall bladder, pancreas, appendix, liver, kidneys, blood, and bone. More than half of the patients (41 of 73) described in Table 4 had diarrhea before onset of extraintestinal disease. Out of 73 cases, 17 patients were <1 year of age, 8 were >60 years old and 18 had an underlying medical problem.

Campylobacter septicemia was particularly prominent in immunocompromised individuals (Table 4). Dhawan et al. (*51*) reviewed 33 cases of *C. jejuni* septicemia: 73% of the patients had diarrhea before onset of septicemia, 36% of the patients were <1 year old, 24% were >50 years old, and more than half of the patients had an underlying immunosuppressive condition. In patients with *C. jejuni* enteritis, septicemia is apparently more common in individuals at the extremes of age or who are immunocompromised (*51*).

Both *C. jejuni* and *C. coli* are susceptible to the bactericidal action of normal human serum; this lack of resistance to serum results in the infrequency of bacteremia and systemic infections except when the host is immunocompromised (22). Perlman et al. (*178*) described an HIV patient simultaneously infected with *C. jejuni* in the blood system and *C. coli* in the gastrointestinal tract. Both *Campylobacter* species isolated from the patient were killed by normal human serum, but only the *C. coli* isolate was killed by the patient's serum, whereas the *C. jejuni* isolate was resistant.

TABLE 3. *Reported cases of Guillain-Barré syndrome and Miller-Fisher syndrome following* Campylobacter *gastroenteritis*

Reference	No. of cases (sex), age	Diarrhea	*C. jejuni* isolated	Comments
GUILLAIN-BARRE SYNDROME				
(190)	1 (M), 47y[a]	+	Stool	*Campylobacter* species not specified
(167)	1 (M), 42y	+	Stool	
(221)	1 (M), 16y	+	Stool	
(183)	1 (M), 34y	+	Stool	
	1 (F), 22y	+	Stool	
(28)	1 (F), 28mo	+	Stool	*Campylobacter* species not specified
(124)	1 (M), 69y	+	Stool	
(220)	2 (M), 38y and 81y	+	Stool	
	I (M), 60y	+	----[b]	Seropositive for *C. jejuni*
(193)	2 (F), 63y and 74y	+	Stool	
	2 (M), 32y and 19y	+	Stool	
(42)	2 (M), 30y and 62y	+	Negative	Seropositive for *C. jejuni*
	1 (M), 74y	+	Negative	Seropositive for *C. jejuni*
(266)	1 (M), 25y	+	----	Seropositive for *C. jejuni*
	1 (F), 83y	+	----	Seropositive for *C. jejuni*
(134)	6 (M), 7y-14y	+	Stool	
	1 (F), 9y	+	Stool	
(55)	1 (M), 17y	+	----	Seropositive for *C. jejuni*
(229)	1 (F), 4y	+	Stool	
(92)	1 (M), 57y	+	Blood	Stool not cultured, patient had graft vs host reaction after allogenic bone marrow transplant
MILLER-FISHER SYNDROME				
(43)	1 (F), 34y	+	Stool	*Campylobacter* species not specified
(256)	1 (M),27y	+	Stool	
(192)	2 (M), 37y and 28y	+	Stool	
(123)	1 (M), 19y	+	----	Seropositive for *C. jejuni*

[a] abbreviations: d, day; mo, month; y, year; M, male; F, female.

[b] Stool not cultured.

ECONOMIC CONSIDERATIONS OF *CAMPYLOBACTER*-INDUCED DISEASES

The estimated number of yearly foodborne cases of *Campylobacter* gastroenteritis, the cost per case and the total costs of the disease in the United Kingdom, Canada, and the United States are presented in Table 5. The number of cases estimated by Franco (*72*) and Lin et al. (*145*) for the United States is 12- to 14-fold higher than that of Todd (*239*). The cost estimate of Franco (*72*) was $3,983 million and that of Lin et al. (*145*) was $907 to 1,016 million for *C. jejuni* gastroenteritis in the United States. These estimates are 6- to 26-fold higher than Todd's (*239*) estimate of $156 million (Table 5).

Not included in these estimates are the costs of GBS, reactive arthritis, and other sequelae of campylobacteriosis. The annual incidence of *C. jejuni* gastroenteritis is estimated to be 1,000 per 100,000 population while the annual incidence of GBS in the United States due to *C. jejuni* is believed to be 0.17 to 0.51 cases per 100,000 people (*165*). Thus, with a total United States population of 253 million in 1991 (243), 430 to 1,290 GBS cases due to *Campylobacter* would have been expected. Little information exists concerning the medical costs of GBS; however, a course of treatment with plasmapheresis for a GBS patient can range from $6,000 to $12,000 while treatment with intravenous immunoglobulin can range from $5,000 to $12,000 (*237*). While no information is available for the incidence of *Campylobacter*-induced reactive arthritis in the United States, reactive arthritis was found in 2.3% of the individuals with positive stool cultures in a recent *Salmonella typhimurium* outbreak; the incidence of Reiter's syndrome was approximately 10-fold less (*9*). Assuming that *Campylobacter* is similar to *Salmonella* in inducing reactive arthritides and using the 2.3% figure, the number of individuals in the United States with *Campylobacter* gastroenteritis leading to reactive arthritis or Reiter's syndrome could range from approximately 4,000 to 50,000 depending on the estimated number of *Campylobacter* cases (Table 5). The costs of other diseases which can be sequelae

of *Campylobacter* infection (Table 4) have not been determined but could be substantial. Costs to patients suffering from nonintestinal diseases resulting from *Campylobacter* infection would be considerably higher than those with only gastroenteritis, since convalescence would be protracted. *Campylobacter*-related diseases are expensive and economic considerations indicate that the presence of the organism in food and water either be prevented or substantially reduced.

CONCLUSIONS

C. jejuni has moved from relative obscurity in the 1970s to a prominent position as a foodborne diarrheic pathogen in the 1990s and is the most common bacterial cause of enteritis in the United States (*233*). However, *C. jejuni* can not be dismissed as only a cause of a temporary, inconvenient gastrointestinal infection. It is now realized that *C. jejuni* is a cause of GBS, reactive arthritis, and Reiter's syndrome. These diseases can lead to long-term illnesses with consequent loss of productivity and diminished quality of life. In addition, *C. jejuni* may induce extraintestinal infections which may involve many organs of the body and even result in death. While nongastroenteritis complications due to *C. jejuni* occur infrequently and only affect a small percentage of the United States population, the number affected is still substantial. Most of the burden to the public from infection by *C. jejuni* is economic: the cost of gastrointestinal illness induced by the organism is enormous and if that cost is coupled with the presently unknown costs of *C. jejuni* complications, the economic liability is unacceptably high.

TABLE 4. *Extraintestinal manifestations associated with* Campylobacter jejuni

Disease or syndrome	No. cases (sex), age	Diarrhea	*C. jejuni* isolated	Comments (reference)
Meningism (pseudomeningitis: irritation of brain or spinal cord membrane but no inflammation)	1 (M), 29y	+	Stool	(*254*)
	1 (M), 12y	+	Stool	(*254*)
Meningitis (inflammation of membranes of brain or spinal cord)	1 (M), 34y	?	CSF	Catheter in ventricular system of brain (*172*)
	1 (M), 12d	-	CSF	A sibling and the mother had diarrhea before baby was born (*235*)
	11 (7 F; 4 M), 5d–15d	-	Blood (5), CSF (2), stool (2)	All 11 patients were seropositive for *C. jejuni*; diarrhea not present in family members (*81*)
Convulsions	1 (M), 14mo	+	Stool	(*255*)
	1 (F), 4y	+	Stool	(*255*)
	9 (??), 3y3mo–7y7mo (mean age 5y8mo)	+	Stool	(*99*)
	1 (M), 14mo	+	Stool	(*217*)
Encephalopathy (disease of the brain)	1 (M), 6y	+	Stool	(*143*)
	1 (M), 13y	+	Stool	(*132*)
Cholecystitis (inflammation of the gall bladder)	1 (F), 52y	+	Stool, bile	(*161*)
	1 (M), 62y	-	Bile	(*54*)
	1 (F), 18y	+	Stool	(*57*)
Erythema nodosum (inflammatory dermatosis with formation of painful nodules on extremities)	1 (F), 24y	+	Stool	(*61*)
	1 (M), 30y (*C. coli*)	-	Stool	(*201*)
	1 (F), 48y	+	Stool	(*136*)
Splenic rupture and abdominal aortic aneurysm	1 (M), 71	+	Stool	(*75*)
Pancreatitis	1 (F), 21y	+	Stool	(*27*)
Appendicitis	1 (M), 16y	?	Appendix	(*39*)
Hepatitis	1 (M), 52y	+	Stool	Had extrinsic asthma (*188*)

Disease or syndrome	No. cases (sex), age	Diarrhea	*C. jejuni* isolated	Comments (reference)
Glomerulonephritis (renal disease with bilateral inflammatory changes in glomeruli)	1 (M), 33y	+	Stool	(*149*)
Triad of glomerulonephritis, pulmonary hemorrhage and anemia	1 (F), 5y	+	Stool	*C. jejuni* antigen present in glomeruli (*8*)
Bursal infection	1 (M), 81y	-	Bursa	(*202*)
Bilateral abducens paresis (paralysis of external oculomotor nerve to external rectus muscle, which turns the eyeball outward)	1 (F), 12y	+	Stool	(*133*)
Septicemia	1 (F), 18mo	-	Blood	Other household members did not have diarrhea (*51*)
	1 (F), premature	-	Blood	Mother had diarrhea before baby was born (*51*)
	1 (F), 6d	+	Blood	Mother had diarrhea before baby was born (*51*)
	1 (M), 62y	-	Blood	Had alcoholic cirrhosis and congestive heart failure (*51*)
	1 (??), 2d (*C. coli*)	+	Stool, blood	Baby had jaundice (*89*)
	1 (M), 41y	+	Stool, blood	Patient had alcoholic related diseases: jaundice and chronic liver disease (*89*)
	1 (M), 33y	-	Blood	Had enteric fistula (*89*)
	70			
	1 (W), 61y	-	Blood (*C. coli*)	Had colonic adenocarcinoma (*89*)
	1 (M), 15y	+	Stool, blood	Had hemophilia (*89*)
	2 (M), 29y and 36y	+	Blood (2), Stool (1)	Both had diarrhea; both were intravenous drug users and both had HIV with severe immunosuppression (*89*)
	1 (F), 26y	-	Blood, stool	Patient had multisystem lupus erythematosus and was deficient in IgA and IgM; on hemodialysis (*108*)
	1 (F), 26y	-	Blood, stool	Recent trip to Sri Lanka (*223*)
	1 (M), 65y	-	Blood	Stool not cultured; had vascular disease (*223*)
	1 (F), 18y	+	Blood, stool	(*223*)
	2 (M), 74y and 31y	+	Blood, stool	On corticosteroid therapy (*223*)
	1 (M), 22y	-	Blood, stool	(*223*)
	1 (M), 70y	-	Blood, stool	Had vascular disease (*223*)
	1 (M), 25y	-	Blood	Stool negative; had agammaglobulinemia (*223*)
	1(F), 31y	+	Blood (*C. coli*)	Stool not cultured; recent trip to India (*223*)

TABLE 4. *Extraintestinal manifestations associaied with* Campylobacter jejuni

Disease or syndrome	No. cases (sex), age	Diarrhea	*C. jejuni* isolated	Comments (reference)
	1 (M), 29y	-	Blood (*C. coli*)	Stool not cultured; had agammaglobulinemia (*223*)
Osteitis (inflammation of bone)	1 (M), 57y	+	Blood	Had diarrhea prior to presentation but stool was negative (*176*)
Hemolytic-uremic syndrome	1 (M), 4mo	+	Stool	(*94*)
	1 (M), 7mo	+		Stool negative, seropositive for *C. jejuni/coli* (*50*)
	1 (M), 57y	+	Stool	Chronic alcoholism with alcoholic pancreatitis (*49*)
	1 (F), 37y	+	Stool	Seropositive for *C. jejuni* (*38*)
	1 (F), 27mo	+		Seropositive for *C. jejuni* but stool was negative, *C. jejuni* isolated from stool of 9mo old asymptomstic male sibling who was also seropositive. This patient was daughter of above female patient (*38*)
Abortion	1 (F), 23y	-	Blood	~14 weeks gestation (*78*)
Premature labor	1 (F), 21y	-	Stool	*C. jejuni* not present in blood of mother, ~30 weeks gestation; baby had *C. jejuni* in blood and ear and died on 34th day (*163*)
Urinary infection	1 (M), 77y	-	Urine	Organism identified as *C. jejuni/coli* (*46*)

[a]abbreviations: d, day; mo, month; y, year; M, male, F, female, CSF, cerebral spinal fluid.

TABLE 5. *Estimated costs of foodborne* Campylobacter *gastroenteritis*

Country, no. cases/year	Cost/case	Total cost in millions	Reference
United Kingdom, 30,000	£587[a]	£18[a]	(*189*)
Canada, 16,450	$925[b]	$15[b]	(*238*)
United States, 170,000	$920[c]	$156[c]	(*239*)
United States, 2,390,000	$1290[c]	$3,983[c]	(*72*)
United States, 2,100,000	$432–484[c]	$907–1,016[c]	(*145*)

[a]British pounds.
[b]Canadian dollars.
[c]United States dollars.

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